PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PCA21266/HMY	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR02/02434**	International filing date *(day/month/year)* 26 DECEMBER 2002 (26.12.2002)	Priority date *(day/month/year)* 09 JANUARY 2002 (09.01.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07D 309/06

Applicant

HANMI PHARM. CO., LTD. et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
21 JULY 2003 (21.07.2003)	30 DECEMBER 2003 (30.12.2003)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR02/02434

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[ ] the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

[ ] the claims:
pages _____, as originally filed
pages _____, as amended (together with any statment) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

[ ] the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

[ ] the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application(under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained inthe international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages _____

[ ] the claims, Nos. _____

[ ] the drawings, sheet _____

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION

tional aplication No.
PCT/KR02/02434

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1 - 8	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 8	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 8	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are referred to:

D1: WO-A-99/65892
D2: WO-A-2001/45484

1. Novelty

D1 and D2 disclose methods for preparing simvastatin of formula I, which is the final product of the present invention, with lovastatin as starting material. D1 is a method of directly introducing methyl group without hydrolyzing 8'-methylbutyryloxy group of lovastatin, which is different form the present invention in reaction mechanism. D2 is the same as the present invention in hydrolysis of 8'-methylbutyryloxy group with lactone ring, but is different from the present invention in that the present invention uses a mixed solvent of potassiumhydroxide-methanol-water as a base in hydrolysis step for producing triol acid of formula III, whereas D2 uses potassium t-butoxide.

Therefore, the subject matter of claims 1 to 8 seems to be novel (PCT Article 33(2)).

2. Inventive Step

For the analysis of the inventive step, D2 is considered the closest prior art. The preparation method of the present invention is different from that of D2 in that D2 relates to a method of preparing protected simvastatin by proceeding reaction by using potassium-t-butoxide in an organic solvent in hydrolysis of reaction step (i), and also using acyloxytriphenylphosphonium salt with a base in acylation step of reaction step (iii), whereas the present invention relates to a method for preparing protected simvastatin by using a mixed solvent of potassiumhydroxide-methanol-water in hydrolysis corresponding to the reaction step (i) of D2 and also using a quaternary ammonium halide or a quaternary phosphonium halide, a catalyst, in acylation reaction.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

Box V

Though both the present invention and the invention of D2 are of the same in the reaction material, intermediate, reaction step, but are different from each other in the catalyst used in each reaction step. Such a difference results in the present invention having no problem of D1: using potassium-t-butoxide, an expensive reagent. In addition, this difference gives the present invention an effect that it does not need to remove triphenylphosphine and unreacted 2,2-dimethylbutaonic acid, which are byproducts of acylation step. Further, such constitution of the present invention cannot be easily invented by a person skilled in the art by using the teaching of D2.

Therefore, the subject matter of claims 1 to 8 does involve an inventive step in the sense of PCT Article 33(3).

3. Industrial Applicability

Claims 1 to 8 meet the criteria set out PCT Article 33(4).